## REMARKS/ARGUMENTS

The present application previously included claims 46-188, and was the subject of both a restriction requirement and an election of species. Applicant responded to both requirements with traverse, but the restriction and election have been maintained. Elected claims 46-89 have therefore been examined, based on the species Pluronic F68 as the surfactant. The examined claims have been rejected under §103, and Applicant hereby responds to the stated rejections. Applicant further submits that the claims are allowable over the cited art, and that consideration of the non-elected species is in order.

Claims 46-50, 57-60 and 63-64 have been rejected under §103(a) as being unpatentable over Skrabanja et al. (USPN 5,929,028) in view of Koll et al. (USPN 6,346,274). The Office Action proposes that it would have been obvious to interchange a surfactant from Koll with a surfactant disclosed in Skrabanja to arrive at the present invention, and Applicant respectfully disagrees for reasons set forth herein.

The Skrabanja patent discloses liquid gonadotropin-containing formulations characterized in that the formulation comprises stabilizing amounts of (a) a polycarboxylic acid or a salt thereof and (b) a thioether compound. As the Office Action indicates, Skrabanja mentions the optional inclusion of one or more nonionic surfactants such as Polysorbate 20, NF (Tween 20), Polysorbate 80, NF (Tween 80), Brij 35, and Pluronic F123. While Skrabanja therefore discloses the potential use of Pluronic F123, Skrabanja does not disclose any of the pluronic surfactants claimed in the present application, namely F68, F77, F87 or F88.

The Koll patent discloses microparticles containing polypeptides for parenteral administration. The microparticles comprise an ABA triblock copolymer, and are intended thereby to keep the aggregation of the active substance as low as possible. Koll mentions FSH as a possible active ingredient in a very long list spanning from column 4, line 51 to

column 5, line 9. This listing is simply indicated as noting "[p]olypeptides which come into consideration within the sense of the invention." Column 4, lines 51-52. The peptide erythropoietin (EPO) is clearly the preferred target of the Koll patent, and is the only subject of the several described Examples.

Moreover, the focus of the Koll patent is on the preparation of microparticles containing an ABA triblock copolymer, with which a large, laundry list of additives may be included. This listing includes serum proteins, polyamino acids, cyclodextrins, cyclodextrin derivatives, saccharides, amino sugars, amino acids, detergents or carboxylic acids, as well as mixtures of these additives. See the Abstract, lines 8-12, and column 8, lines 4-11. Given this long and diverse listing, and the single additive EPO described in the Examples, the Koll patent cannot fairly be said to teach specific combinations of the multitude of additives mentioned therein. More specifically, Koll cannot be said to teach the combination of Pluronic 68 (or Pluronic F77, Pluronic F87 or Pluronic F88) specifically with FSH or a variant thereof. Koll discloses a wealth of excipients that may be optionally used, and in that context mentions also detergents such as Tween 20, Tween 80 and pluronics as a class. But the general description does not contain any teaching as to which detergent/surfactant to choose for which peptide, and it is silent on Pluonic F68.

Pluronic F68 is only mentioned once in Koll, namely in Table 1 in a very specific combination with EPO. Table 1 simply presents that the use of Pluronic F68, and numerous other additives, with ABA triblock copolymer microparticles containing EPO resulted in a reduction in the aggregation of the microparticles. Tween 20 and Pluronic F127, at the same w/w % level, provided a similar reduction in aggregation of the ABA microparticles. Thus, a person skilled in the art would not even know from Koll whether Pluronic F68 had any advantageous effects over Tween 20 or Pluronic F127 with respect to the specific

combination of EPO on ABA microparticles. It certainly is impossible to conclude from Koll whether Pluronic F68 would be an appropriate surfactant for any other peptide such as FSH.

It is therefore submitted that the skilled person would not have had an incentive to replace Pluronic F123 in Skrabanja with the Pluronic F68 (or Pluronic F77, Pluronic F87 or Pluronic F88) in view of Koll because the only reference to Pluronic F68 is in respect to EPO. EPO is a compound which is completely unrelated to gonadotropins. The skilled person knows that surfactants may have very different effects depending on the active ingredients with which they are combined. Submitted herewith is an extract from Akers, Journal of Pharmaceutical Sciences, Vol. 91, No. 11, November, 2002, for example, which clearly shows on pages 228and 2286 that Tween 20, while avoiding aggregate formation of recombinant human factor VIII, induces aggregates of another protein (Hunicola lanuginose lipase). The skilled person would thus not have been motivated to replace Pluronic F123 in Skrabanja with the Pluronics F68, F77, F87 or F88.

This is even more so, as the skilled person is aware of the very different properties of Pluronic F123 on the one hand, and Pluronic F68, F77, F87 and/or F88 on the other hand. We draw the Examiner's attention to the structures and properties of these different surfactants. Pluronic F68 has the formula $EO_{78}PO_{30}EO_{78}$ (wherein EO means ethylene oxide and PO means propylene oxide). Pluronic F68 is primarily made up of hydrophilic ethylene oxide groups and, as stated in the present application, it is 80% hydrophilic. (Pluronics F77, F87 and F88 are also highly hydrophilic – between 70% and 80% - and thus have very similar properties to F68.) To the contrary, Pluronic F123 has the formula $EO_{19}PO_{69}EO_{19}$. It is thus highly hydrophobic and has completely different physico-chemical properties from F68.

It is therefore apparent that Pluronic F123 does not have the same effects as the Pluronics F68, F77, F87 or F88. Thus, while F123 may be said to generally fall within the

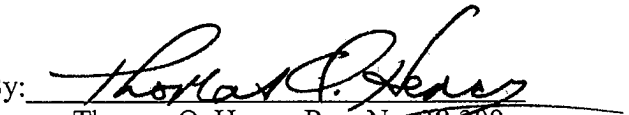
"genus" of pluronic surfactants, it is seen to be significantly different in physico-chemical properties due to its contrasting hydrophobic nature. The skilled person would not have had any incentive to replace F123 of Skrabanja by pluronics with completely different properties.

Claims 51-56, 61-62, 79-81 and 86-87 have been rejected based on the foregoing combination of Skrabanja and Koll, and further in view of Hoffman et al. (EP 0 974 359). However, as these claims are all dependent on the claims already discussed, they are submitted to be non-obvious for the same reasons.

The Office Action suggests that it would have been obvious to one of ordinary skill in the art to replace the disclosed Pluronic F173 with the claimed surfactant Pluronic F68. Applicant submits, however, that it would not have been obvious to make the asserted substitution for the reasons, *inter alia*, that the teachings of Skrabanja and Koll are quite different, and the Pluronic F173 surfactant disclosed in Skrabanja is significantly different from the pluronic surfactants claimed herein, including specifically Pluronic F68.

Reconsideration of the above-identified patent application, as amended and in view of the foregoing remarks, is respectfully submitted. An action on the merits and allowance of the claims is solicited. If the Examiner believes that it would expedite examination of this case, the Examiner is requested to contact the undersigned directly.

Respectfully submitted,

By: 

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